MEDICAMENT RESPIRATORY DELIVERY DEVICE AND METHOD

RELATED APPLICATIONS

[00001] This Application is a continuation application of Serial No. 09/950,369 filed September 10, 2001, which is a continuation-in-part application of Serial No. 09/879,517 filed June 12, 2001, which is a continuation-in-part application of Serial No. 09/758,776 filed January 12, 2001, all three of which are herein incorporated by reference.

FIELD OF THE INVENTION

[00002] This invention relates to medicament respiratory delivery devices, including pulmonary, intranasal and buccal respiratory delivery devices, which releases and delivers on demand a controlled unit dose of aerosolized medicament to the respiratory system of a patient and method of delivery.

BACKGROUND OF THE INVENTION

[00003] Inhalers and atomizers are now commonly used primarily to deliver various liquid medicaments via the patient's or user's nose or mouth. As used herein, "medicament" includes any powder or liquid medicament, drug or vaccine or combinations thereof which may be administered from an respiratory delivery device through the user's nose or mouth, sometimes referred to herein as a medicament respiratory delivery device. More recently, the prior art has proposed unit dose disposable powder medicament delivery devices, such as disclosed in U.S. Patent No. 5,215,221, wherein a predetermined quantity or unit dose of a powder medicament is sealed in a reservoir formed between opposed thermoplastic sheets and expressed or delivered by application of manual force to a thermoformed blister which, upon

activation, breaks a burstable seal between the sheets at the entrance to the reservoir and fluidizes the powder medicament in the reservoir through a delivery tube. The sealed delivery tube is cut prior to use.

[00004] There are several considerations affecting the design and efficacy of medicament respiratory delivery devices. First, it is important to ensure that a predetermined quantity or dose of medicament is consistently delivered to the user with each application. Second, because respiratory therapy often requires numerous applications, the cost of providing the dosage should also be considered. Thus, it is desirable that the medicament respiratory delivery device consistently express substantially all of the medicament to the user and that the delivery device is not susceptible to user error in operation. Third, it is important that the medicament be properly disbursed or entrained in the conveying fluid. Further considerations include the operating complexity, cost of the device, portability and size of the delivery device. It would also be desirable in certain applications to provide a reusable delivery device with a disposable standard medicament cartridge containing a unit dose of medicament which can be easily handled and replaced in the delivery device by the user without error. In other applications, a disposable delivery device is desirable.

[00005] Further, it would be desirable for a respiratory delivery device to deliver a controlled unit dose of an aerosolized medicament on demand. That is, it would be desirable to be able to charge or pressurize the medicament respiratory delivery device prior to use, such that the patient does not have to simultaneously manipulate the pressure delivery means, as by compressing a bulb or syringe, with the mouth or nosepiece in the patient's mouth or nose, while inhaling the aerosolized

medicament. This can be difficult for some patients to accomplish and may result in poor or partial delivery of the medicament.

[00006] The medicament respiratory delivery device of this invention provides a reproducible, high level of clearance of medicament or emitted dose from a replaceable cartridge, wherein a manually actuatable fluid pressure delivery device may be charged prior to use and then released on demand to deliver a controlled unit dose of an aerosolized medicament to the respiratory system of the patient.

SUMMARY OF THE INVENTION

[00007] As set forth above, the medicament respiratory delivery device of this invention may be utilized for pulmonary, intranasal, and buccal respiratory delivery of medicaments, drugs or vaccines and various combinations thereof. The medicament respiratory delivery device of this invention includes a medicament housing including a chamber having a chamber inlet and preferably a generally coaxially aligned chamber outlet, a medicament cartridge is preferably located within the housing chamber having opposed ends, a passage through the cartridge through the opposed ends generally coaxially aligned with the chamber inlet and outlet of the housing, a medicament in the cartridge passage and a burstable membrane sealing the passage preferably at both ends of the cartridge having a burst pressure of less than 10 atmospheres. The medicament respiratory delivery device further includes a manually actuatable fluid delivery device having an outlet in fluid communication with the chamber inlet for delivery of fluid under pressure to the chamber and a valve located between the outlet of the fluid delivery device and the chamber inlet including a valve inlet in fluid communication with the outlet of the fluid delivery device and an outlet in fluid communication with the chamber inlet of the medicament housing.

[00008] Upon actuation of the manually actuatable fluid delivery device, fluid is delivered under pressure to the valve, thereby charging the medicament respiratory delivery device for use. Then, upon opening of the valve, fluid is delivered under pressure to the inlet of the chamber containing the cartridge, thereby rupturing the burstable membranes of the cartridge and expressing the medicament through the chamber outlet. In the preferred embodiment, the manually actuatable fluid delivery device is actuatable to maintain the fluid pressure at the outlet, prior to opening of the valve, to permit the user to release the manually actuatable fluid delivery device and insert the housing outlet into the nose or mouth.

[00009] The medicament respiratory delivery device of this invention thereby separates the charging or pressurizing function from the use function. That is, the medicament aerosol delivery device of this invention may be utilized by a patient to first "arm" or pressurize the valve inlet and then deliver fluid under pressure to the housing chamber containing the cartridge by opening the valve. Thus, for example, the patient may first arm the medicament respiratory delivery device of this invention by manipulating the pressure delivery device to pressurize a chamber at the valve inlet, then turn the device to receive the mouthpiece or nosepiece in the user's mouth or nose and then open the valve to deliver a controlled unit dose of an aerosolized medicament to the respiratory system of the patient through the nose or mouth. This simplifies the operation and use of the device to minimize user error and consistently deliver a predetermined quantity or dose of medicament to the patient's respiratory system.

[00010] As will be understood by those skilled in this art, various fluid delivery devices and valves may be utilized in the medicament respiratory delivery device of this invention. For example, the fluid delivery device may include a

collapsible bulb which communicates with a pressure chamber through a one way valve having an outlet in communication with the valve inlet. However, in a preferred embodiment of the medicament respiratory delivery device of this invention disclosed herein, the manually actuatable fluid delivery device includes a tubular pressure member having an outlet and a plunger or stopper received in the tubular pressure member in sealed relation which is manually reciprocable in the tubular pressure member toward the pressure member outlet. The manually actuatable fluid delivery device may be a conventional syringe preferably having finger grips and a plunger and stopper assembly, such that the patient can hold the barrel and manipulate the plunger with the patient's thumb. Thus, upon movement of the plunger, the stopper is moved in sealed relation toward the syringe outlet, pressurizing the fluid, preferably air, at the syringe outlet. Opening of the valve at the pressure member outlet thus releases or expresses the fluid into the housing chamber containing the cartridge, rupturing the burstable membrane and delivering the medicament to the outlet of the housing as described. In the preferred embodiment, the plunger and stopper assembly and tubular barrel include cooperative stop members which releasably retain the stopper in the barrel when the stopper is moved in the tubular barrel to generate sufficient pressure at the syringe outlet to rupture the burstable membranes. In the disclosed embodiment, the valve is a conventional Schraeder valve operable at pressures of 10 atmospheres or less having a valve stem extending toward the housing, such that movement of the housing toward the manually actuatable fluid delivery device opens the valve and delivers the fluid under pressure to the housing chamber inlet. In the preferred embodiment, the housing includes a bar or finger in the inlet, such that the finger or bar engages the valve stem when the housing is moved toward the manually actuatable fluid delivery device

or syringe; however, the valve stem may also engage directly against the burstable membrane at the inlet of the cartridge. Alternatively, the valve stem may extend into the syringe barrel for engagement by the stopper as described further below. As will be understood, however, the valve may be any suitable valve, preferably a manually actuatable valve as discussed further below.

[00011] In the disclosed embodiment of the medicament respiratory delivery device of this invention, the plunger comprises two telescopic tubular members including a plunger affixed to the stopper and a tubular piston housing which telescopically receives the plunger and the plunger is resiliently biased by a coil spring or the like. The plunger and stopper assembly is assembled by inserting the plunger into the tubular piston housing, compressing the spring and locking the members together by a detent on the plunger which is received in a detent pocket on the tubular piston housing with the spring partially compressed. Then, upon opening of the valve, the sudden drop in pressure allows the spring to drive the stopper to the outlet of the syringe barrel, sweeping the remaining fluid in the barrel through the valve.

[00012] As set forth above, in the preferred embodiment of the medicament respiratory delivery device of this invention, the manually actuated fluid delivery device is actuatable to maintain the fluid pressure at the outlet prior to opening of the valve to permit the user to release the fluid delivery device and insert the medicament housing outlet into the nose or mouth prior to opening of the valve. In the disclosed embodiment, wherein the manually actuatable fluid delivery device comprises a tubular pressure member, such as a syringe barrel, and a plunger or stopper, interlocking stop members are provided on the syringe barrel and the plunger and stopper assembly which allow the user to fix the plunger when the pressure at the

syringe outlet is sufficient to rupture the burstable membranes of the medicament cartridge. This allows the user to fix the stopper in the syringe barrel and maintain the pressure at the syringe barrel outlet while turning the device to receive the outlet of the medicament housing in the nose or mouth prior to opening the valve. In the disclosed embodiment, the valve is a conventional Schraeder valve having a projecting valve stem and the medicament housing is moveable relative to the manually actuatable fluid delivery device to depress the valve stem and open the valve.

[00013] The cartridge for the medicament respiratory delivery device of this invention is preferably simple in construction, inexpensive and disposable, such that the delivery device is reusable by inserting a new cartridge in the housing chamber following each use. However, the cartridge may be eliminated in a nonreusuable delivery device wherein the burstable membranes are provided at the inlet and outlet to the housing chamber. In the preferred embodiment of the medicament respiratory delivery device of this invention, the medicament cartridge includes a body having opposed ends, a passage through the body and through the opposed ends, a medicament stored in the passage and burstable or pierceable membranes covering and sealing the passage at the opposed ends of the body. In the preferred embodiments, the opposed ends of the cartridge body surrounding the passage are convex and the burstable membranes are stretched taut over the convex opposed ends and bonded thereto, sealing the passage. In the disclosed embodiment, the opposed ends of the body are frustoconical surrounding the passage and the membranes comprise a thin polyolefin film heat-sealed or fused to the opposed frustoconical ends of the body. The term polyolefin is understood to mean a polymer containing olefin units such as, for example, ethylene, propylene or 1-butene units or any other alpha-olefin. Polyolefin as

used herein includes polyethylene, polypropylene, ethylene- .alpha. olefin copolymer, wherein the alpha olefin having from 3 to 20, preferably 4 to 8 carbon atoms, polyolefin copolymers made by polymerizing olefins in the presence of a metallocene catalyst, ethylene-vinyl acetate copolymer, ethylene-ethyl acrylate copolymer, and ethylene-methyl acrylate copolymer. In particular, it is desirable to use polyethylene, such as low-density, linear-low-density, very-low-density, medium-density, or high-density polyethylene, or polypropylene, such as a polypropylene homopolymer, ethylene-propylene copolymer, or ethylene-propylene block copolymer.

[00014] In one preferred embodiment, the polymeric films which form the burstable membranes are preferentially or uniaxially oriented polyolefin films, preferably oriented polyethylene films, angularly related, wherein the films oriented on the opposed ends of the cartridge are most preferably oriented at approximately right angles. It has been found by the applicant that burstable membranes formed of preferentially or uniaxially oriented polyolefin film, most preferably polyethylene film, wherein the films are oriented at approximately right angles, results in improved delivery of the medicament from the body chamber of the delivery device to the respiratory system of the user and results in a consistently greater emitted dose. Polyolefin films can be oriented by drawing in one or both mutually perpendicular directions in the plane of the film to impart strength thereto using methods known in the art. Oriented polyolefin films include machine direction and transverse direction orientation. Oriented polyolefin films include uniaxially or biaxially oriented films, with uniaxially films being preferred having a draw ratio of at least 1.2. Uniaxially-oriented films have properties to their advantage for use as the burstable membranes, including relatively high stiffness, as indicated by the tensile modulus in a particular

direction, usually the machine direction, compared to the transverse direction. Properties of the oriented polyolefin film can be dependent to a certain degree on the particular process conditions under which the polyolefin film was manufactured. For example, a stiffer film with lower transverse burst pressure properties would result from an orientation process incorporating a larger machine direction orientation draw ratio. Thus, oriented polyolefins films can be tailored to provide an appropriate burst pressure property within a preferred film thickness range.

[00015] Based upon computer modeling by the applicant, consistently greater dosing is believed to result from turbulence or "turning" of the delivery fluid through the passage of the cartridge containing the medicament where preferentially oriented polyolefin membranes are used oriented at approximately right angles on the opposed ends of the cartridge. Prototype testing indicates that the burstable membranes at the opposite ends of the cartridge in the delivery devices of this invention rupture nearly simultaneously using only a modest pressure, *e.g.*, less than 5 atmospheres. Where the membranes are preferentially or uniaxially oriented and perpendicular, the membranes each rupture in a slit near the center along the axis of the oriented films at approximately right angles to one another. This requires the fluid, such as a gas, to turn as the fluid is rapidly transmitted through the passage, entraining the medicament and expressing the entrained medicament through the slit formed in the second membrane. It has been found by the applicant that generally perpendicular orientation of the preferentially or uniaxially oriented films oriented at right angles resulted in an emitted dose of about 97%.

[00016] In another preferred embodiment, the burstable membranes are formed of a cast polyolefin copolymer of polyethylene and polyethylene methylacrylate

copolymer film having a thickness of about 0.5 mil, wherein the films are stretched taut over the passage and heat sealed or fused to the opposed ends of the cartridge. Where the burstable membranes are formed of preferentially or uniaxially oriented polyethylene film, the film preferably has a thickness of about 1 mil. However, it is believed that the burstable membranes may also be formed of other polymers including, for example, polypropylene, acetate, polycarbonate, etc., wherein the film is preferably scored or embossed to reduce the required gas rupture pressure, thus having a rupture pressure of between 1.2 and 10 atmospheres, more preferably less than 5 atmospheres and most preferably between 1.5 and 4 atmospheres. Medicament cartridges employing such low burst pressure films allow for use of simple, manually actuated, pressurization mechanisms as described below. In the preferred embodiment of the cartridge for a medicament delivery device of this invention, the medicament passage or reservoir is generally cylindrical and the cartridge body is also generally cylindrical. An annular groove may be provided at the mid-portion of the body for ease of handling.

[00017] As disclosed in the above-referenced co-pending application, U.S. Serial No. 09/879,517, the medicament cartridge utilized in the medicament respiratory delivery device of this invention may be formed by injection molding a generally cylindrical cartridge body having convex end portions and a passage through the end portions. The method then includes applying a thin burstable polyolefin sheet over one end, preferably by stretching a polyethylene sheet over the end and heat bonding the sheet to the convex end of the cartridge body, sealing the first end. The medicament may then be inserted through the open end of the passage and the second end is then sealed as described. Based upon computer modeling by the Applicant, the highest medicament delivery rate is achieved using one burstable polyolefin membrane

at the exit of the delivery device. This can be accomplished by the medicament delivery device of this invention by utilizing the valve stem or another piercing member to pierce the burstable membrane at the inlet prior to or during actuation of the pressure member. However, in the disclosed preferred embodiment of the medicament respiratory delivery device, the opening of the valve substantially simultaneously bursts both the inlet and outlet membranes avoiding any loss of medicament through the inlet membrane during use.

[00018] The preferred embodiments of the medicament delivery device of this invention are particularly, but not exclusively, adapted for respiratory delivery including pulmonary, intranasal or buccal medicament delivery of a powder medicament, wherein the patient's inspiratory flowrate is not the driving force or pressure behind the aerosolization of the powder medicament. The powder is dispersed by fluid pressure that ruptures the membranes on the opposed ends of the cartridge, creating a substantially instantaneous fluid stream through the cartridge, entraining the powder particles into the fluid, which disperses the medicament to the respiratory system of the patient. This allows for less dependence of the aerosolization of medicament on a patient's inspiration rate. As will be understood, however, the medicament respiratory delivery device of this invention, particularly including the cartridge, can also be utilized for liquid medicament delivery.

[00019] Other advantages and meritorious features of the medicament respiratory delivery device of this invention will be more fully understood from the following description of the preferred embodiments, the claims and the appended drawings, a brief description of which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[00020] Figure 1 is an exploded perspective view of one embodiment of the medicament respiratory delivery device of this invention;

[00021] Figure 2A is a partially cross-sectioned side view of one embodiment of the plunger assembly illustrated in Figure 1 prior to assembly;

[00022] Figure 2B is a side cross-sectioned view of the plunger assembly shown in Figure 2A following assembly;

[00023] Figure 3 is a side partially cross-sectioned view of the medicament respiratory delivery device shown in Figure 1 in the "unarmed" state;

[00024] Figure 4 is a side partially cross-sectioned view of the medicament respiratory delivery device shown in Figures 1 and 3 in the "armed" state;

[00025] Figure 5 is a side partially cross-sectioned view of the medicament respiratory delivery device shown in Figures 1, 3 and 4 during expressing of the medicament in the medicament cartridge;

[00026] Figure 6 is a side partially cross-sectioned view of the medicament respiratory delivery device shown in Figures 3 to 5 following delivery of the medicament;

[00027] Figure 7 is a perspective view of the medicament cartridge shown in Figure 1;

[00028] Figure 8 is a side cross-sectional view of the medicament cartridge shown in Figure 7 in the direction of view arrows 8-8; and

[00029] Figure 9 is a partial side cross-sectional view of the detent locking arrangement for the manually actuatable fluid delivery device illustrated in Figures 2A and 2B.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

[00030] The embodiment of the medicament delivery device 20 illustrated in Figure 1 includes a plunger and stopper assembly 22, a barrel and valve assembly 24 and a housing and cartridge assembly 26. The plunger and stopper assembly 22 includes an elastomeric stopper 28 and a plunger or piston 30 having an integral detent 32. A coil spring 34 is received in the open end 35 of the tubular piston housing 36 as described further below and the tubular housing 36 includes a detent pocket 38 and an end wall 40 including radial locking projections or tabs 42 and an integral thumb grip 44.

[00031] The barrel and valve assembly 24 includes a tubular barrel 46 including a reduced diameter tip portion 48 having an open end 49, integral finger grips 50 and an integral flange portion 52 having hook-shaped locking tabs 54. The reduced diameter tip portion 48 of the barrel 46 includes an annular groove 55 which receives an O-ring 57 and integral resilient opposed L-shaped tabs 59. The Schraeder valve 56 is received in the open end 49 of the tip portion 48 and retained therein by a press fit and the valve includes a projecting valve stem 58. The housing and cartridge assembly 26 includes a medicament dosing member comprised of a first housing member 60 having a female threaded opening or bore 62 having axially extending rectangular grooves 63 which receive tabs 59 and a second housing member 64 having a male threaded end portion 66. The first housing member 60 includes a port or passage 68 therethrough which defines the inlet of the medicament dosing member or housing and the second housing member 64 includes a chamber 70 which receives the medicament cartridge 72 coaxially aligned with the passage 68 through the first housing member 60 and a cone-shaped outlet 76, which is also coaxially aligned with the chamber 70 and the passage

68 when the first and second housing members 60 and 64 are threaded together. In a preferred embodiment, the first housing member 60 also includes finger grips 78 which may be integral with the first housing member, as shown. The first housing member 60 further includes an integral bar or finger 69 bridging the internal surface of the inlet opening 68 as best shown in Figures 3 to 6. The finger 69 may be integrally molded with the first housing member by injection molding or a separate finger may be inserted through the wall of the tubular first housing member 60.

[00032] Figures 2A and 2B illustrate the assembly of the plunger and stopper assembly 22. The stopper and plunger assembly 22 is assembled by depressing the stopper 28 against the spring 34 until the detent 32 is received in the detent opening or pocket 38. Figure 9 illustrates in more detail a preferred embodiment of the detent 32 and pocket 38 illustrated in Figures 1 to 3. The resilient detent 32 may be integral with the tubular wall 30 of the plunger and preferably includes a ramp portion 31 and a vertical stop portion 33. The detent pocket 38 in the disclosed embodiment is an elongated rectangular opening in the tubular wall 36 of the piston housing having a length sufficient to allow the plunger 30 and stopper 28 to move from a first position as shown in Figures 4 and 5 to an extended position as shown in Figure 6 as further described below. As disclosed below, the detent 32 moves in the detent pocket 38 upon opening of the valve 56 which results in a sudden drop of pressure between the stopper 28 and the outlet of the syringe barrel to sweep fluid in the chamber 92 through the valve 50 and the passage 84 of the cartridge 72. The barrel and valve assembly 24 is assembled in the housing member 60 of the housing and cartridge member 26 by first inserting the Schraeder valve 56 in the open end 49 of the tubular barrel 46, disposing the O-ring 57 in the annular groove 55 and then inserting the reduced diameter tip

portion 48 into the bore 68 of the housing member 60. During insertion of the reduced diameter tip portion 48 in the bore 68 of the housing member 60, the resilient L-shaped tabs 59 are received in the elongated grooves 63 in the bore 68 which slidably locks the housing member 60 on the reduced diameter tip portion 48 and prevents rotational movement of the housing member 60 on the barrel 46 following assembly. As described below, the housing member 60 is telescopically moved on the reduced diameter tip portion 48 by the patient to actuate or open the valve 56 and the O-ring 57 adjacent the open end 49 of the reduced diameter tip portion 48 seals the passage between the valve outlet and the medicament cartridge 72. The housing and cartridge assembly 26 is assembled by first inserting the medicament cartridge 72 in the chamber 70 in the second housing member 64 and then threading the male threaded portion 66 into the female threaded portion 62 as shown in Figure 3.

[00033] The assembled plunger and stopper assembly 22 is inserted into the open end 53 of the barrel and valve assembly 24 as shown in Figure 3. As will be understood, the plunger and stopper assembly 22 and the barrel and valve assembly 24 may be assembled in the housing member 60 as described above by the manufacturer of the medicament respiratory delivery device 20 of this invention, such that the patient need only assemble the medicament cartridge 72 in the port or passage 68 following each use by unthreading the housing member 64 from the housing member 60 as described above. The medicament respiratory delivery device is then ready for use.

[00034] Figures 7 and 8 illustrate a preferred embodiment of the medicament cartridge 72, which is disclosed in more detail in the above-referenced co-pending patent application. The medicament cartridge 72 includes a generally cylindrical body 80 which may be formed by injection molding a suitable polymer, such

as polyethylene. The body 80 includes opposed end portions 82 which, in the preferred embodiment, are convex, most preferably frustoconical as shown. The cartridge body 80 includes a cylindrical passage 84 through the end portions 82 and a medicament 88 is disposed within the sealed cartridge. In the disclosed embodiment, the body 80 includes a V-shaped groove 90 for ease of handling because the cartridge is relatively small. The opposed ends 82 of the cartridge are preferably convex such that the burstable membranes 86 may be stretched taut over the surface of the end portions 82 prior to bonding of the membranes to the ends 82 of the cartridge body. Because the burst pressure of the membranes 86 is relatively low, less than 10 atmospheres or more preferably less than 5 atmospheres, the membranes 86 are preferably stretched taut to assure a reproducible rupture pressure as discussed further below. As disclosed more fully in the above-referenced co-pending patent application, the cartridge 72 may be formed by first heat bonding one membrane to one end 82 of the cartridge, wherein the membrane is first stretched taut over the frustoconical end 82 of the cartridge and then heat fused to the cartridge by a suitable die (not shown). The medicament 88 is then inserted into the cartridge through the opposed open end of the passage 84. The opposed end of the passage 84 is then sealed by applying a second burstable membrane to the opposed convex end 82 of the cartridge by stretching the membrane over the frustoconical end and heat bonding the opposed membrane to the opposed end, sealing the cartridge. As set forth above, the medicament 88 may be a fine powder medicament, vaccine or drug or a liquid medicament, drug or vaccine or combinations thereof which may be administered from the respiratory delivery device of this invention through the user's nose or mouth to the patient's respiratory system. Further, the delivery of the medicament to the user is not dependent upon the inspiration of the

user. The delivery device delivers a predetermined quantity or dose of medicament with each application.

[00035] In a most preferred embodiment of the cartridge 72, the burstable membranes 86 are formed from a thin sheet of a polyolefin, most preferably polyethylene, a polyethylene blend or copolymer having a thickness of between 0.5 and 1.5 mils and a burst pressure of less than 10 atmospheres, preferably less than 5 atmospheres, and most preferably between 1.5 and 4 atmospheres. As disclosed more fully in the above-referenced co-pending patent application, the burstable membranes may be formed of a preferentially oriented or uniaxially oriented polyolefin film, wherein the burstable membranes on the opposed ends 82 of the cartridge are oriented at approximately at right angles. As described below, the burstable membranes 86 on opposed ends 82 of the cartridge rupture substantially simultaneously when fluid under pressure is received through the passage 68 of the housing and cartridge assembly 26. Where the burstable membranes 86 comprise preferentially or uniaxially oriented burstable films and the films are oriented at approximately right angles, the films rupture in slits generally at or near the center of the passage 84 along the orientation of the film, causing the fluid, preferably air, to turn through the passage 84, entraining the medicament 88 and expressing the entrained medicament through the perpendicular slit formed in the opposed membrane. It has been found by the applicant that generally perpendicular orientation of the preferentially or uniaxially oriented films, wherein the films are oriented at approximately right angles results in an admitted dose of about 97%. As set forth below, however, other polyolefin films may be used for the burstable membranes 86.

[00036] The next step in charging the medicament respiratory delivery device 20 is driving the plunger and stopper assembly 22 through the tubular barrel 46 toward the reduced diameter tubular tip portion 48 to create a pressure chamber 92 between the stopper 28 and the inlet to the valve 56 as shown in Figure 4. This is accomplished by inserting the thumb of the patient into the thumb grip 44, gripping the finger grips 50 and depressing the thumb. The plunger and stopper assembly 22 is then rotated as shown by arrow 94 in Figure 1, whereby the radial locking tabs 42 are received in the hook-shaped tabs 54, locking the plunger and stopper assembly 22 in the position shown in Figure 4. The medicament respiratory delivery device 20 is thereby armed and ready for expressing the medicament 88 in the cartridge 72 as now described.

[00037] The patient then turns the medicament respiratory delivery device 20 to receive the outlet 76 of the housing and cartridge assembly 26 in the patient's nose or mouth for delivery of the medicament. The patient then grips the finger grip 78 of the housing and thump grip 44 and then compresses the housing and cartridge assembly 26 toward the barrel and valve assembly 24, which causes the bar 69 opposite the valve stem 58 bridging the internal surface of the first housing member 60 to depress the valve stem 58 as shown in Figure 5, opening the valve 56. During telescopic movement of the housing and cartridge assembly 26 toward the barrel and valve assembly 24 as shown by arrows 96 in Figure 5, the L-shaped tabs 59 on the reduced diameter tip portion 48 travel or slide in the elongated grooves or slots 63 in the housing member 60, preferably the full length of the groove 63, such that the groove 63 provide a positive stop for movement of the housing member 60 and prevent rotation of the housing and cartridge assembly 26 on the barrel and valve assembly 24 during actuation of the

valve. Fluid under pressure is then received in the inlet opening 68, substantially simultaneously rupturing the burstable membranes 86 at the opposed ends of the medicament cartridge 72 and expressing the entrained medicament through the outlet 76 as shown by arrows 98 in Figure 5. The sudden reduction of pressure in the pressure chamber 92 (Figure 5) resulting from opening of the valve 56 drives the stopper 28 to the end of the chamber 92 as shown in Figure 6 under the force of the coil spring 34 to sweep remaining fluid in the barrel 46 through the housing and cartridge assembly 26, completing the delivery of medicament to the patient.

[00038] The patient then releases the finger grip 78 and replaces the cartridge 72 for reuse by unthreading the housing member 64 from the housing member 60. Alternatively, the housing member 64 may be releasably interconnected to the housing member 60 by other suitable mechanisms including conventional detents and detent pockets, bayonet connections, etc. Except for the cartridge 72, the medicament respiratory delivery device 20 of this invention is reusable. Further, it should be noted that the cartridge 72 can be inserted into the chamber 70 of the housing and cartridge assembly 26 in either orientation, thereby avoiding error. The medicament respiratory delivery device thereby delivers a controlled dose of a aerosolized medicament on demand. That is, the patient can charge or pressurize the medicament respiratory delivery device prior to use, such that the patient does not have to simultaneously pressurize the pressure delivery device with the mouth or nosepiece in the patient's mouth or nose while inhaling the medicament.

[00039] Prototype testing of the medicament cartridge 72 illustrated in Figures 7 and 8 in a test fixture with perpendicular uniaxially oriented polyethylene films having a thickness of about 1 mil having a burst pressure of about 3 atmospheres

resulted in an emitted dose of about 97% of a powder medicament having a particle size of 1 to 5 microns. Burst tests of burstable membranes were conducted by the Applicant using a syringe as shown to deliver gas under pressure to a cartridge in a test fixture simulating the medicament respiratory delivery devices of this invention. The cartridge was formed as described herein having a surface area of 0.049 in^2 (3mm diameter) covering the passage. The stopper was moved through the barrel under controlled conditions at 25 in/min and the burst pressure (force divided by area) and emitted dose (i.e. percentage of powder emitted from the passage, HPLC assay) was measured. The preferred particle size for intranasal delivery is 50 to 100 microns. 1 to 5 microns is preferred for pulmonary delivery of powder medicament, such as insulin. The applicant also tested other burstable films or membranes with the following results. A cast 50/50 copolymer of ethylene and methylacrylate having a thickness of 0.5 mil and burst pressure of about 2 atmospheres resulted in an emitted dose of about 95%.

[00040] As used herein, "polyolefin" includes polymers derived from simple olefins including polyethylene, polypropylene, polybutenes, etc., copolymers and blends. As used herein, "polyethylene," includes polyethylene blends and copolymers with and without additives. Uniaxially oriented polyethylene films having a thickness of about 0.5 mil having a burst pressure of about 3 atmospheres, wherein the films were oriented approximately parallel, resulted in a 93% emitted dose rate. The applicant also tested a polyethylene film having a thickness of about 0.9 mil wherein the polyethylene film had a checker board embossment having a burst pressure of about 3 atmospheres, wherein the emitted dose rate was about 91%. Thus, the preferred embodiments of the cartridge for a medicament respiratory delivery device of this invention include burstable membranes formed of polyethylene film having a thickness

of between about 0.3 mil to about 1.5 mil, wherein the preferred range is between 0.5 and one mil and a burst pressure of between 1.2 and 10 atmospheres or more preferably less than 5 atmospheres and most preferably between 1.5 and 4 atmospheres. It is believed, however, that films formed of other polymers may be used including, for example, polypropylene, acetate and polycarbonate; however, it is also believed that such other films should be scored or embossed to reduce the burst pressure.

[00041] As will be understood, the medicament respiratory delivery device and cartridge of this invention may be utilized to deliver various substances including medicaments, drugs and vaccines or combinations thereof to the respiratory system via the nasal, pulmonary or buccal routes used in the prevention, diagnosis, alleviation, treatment or cure of diseases. These substances may include, for example, (i) drugs such as Anti-Angiogenesis agents, Antisense, anti-ulcer, butorphanol, Calcitonin and analogs, COX-II inhibitors, desmopressin and analogs, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Growth hormone and analogs (including growth hormone releasing hormone), Growth hormone antagonists, IgE suppressors, Insulin, insulinotropin and analogs, Ketamine, Kytril, Leutenizing hormone releasing hormone and analogs, lidocaine, metoclopramide, Midazolam, Narcotic analgesics, neuraminidase inhibitors, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, vasopressin; (ii) vaccines with or without carriers/adjuvants such as prophylactics and therapeutic antigens (including but not limited to subunit protein, peptide and polysaccharide, polysaccharide conjugates,

toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors) in connection with, arthritis, cholera, cocaine addiction, HIB, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and E, polio, HIV, parainfluenza, rotavirus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhea, asthma, atheroschlerosis, malaria, otitis media, E-coli, Alzheimers, H. Pylori, salmonella, diabetes, cancer and herpes simplex; and (iii) other substances in all of the major therapeutics such as Agents for the common cold, Anti-addiction, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, anti-allergy agents, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, anti-depressants, anti-diuretics, anti-emetics, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations, antinauseants, antineoplastics, anti-obesity, antiosteoporeteic, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antitussiers, anticholinergics, benzodiazepine antagonists, bone stimulating agents, bronchial dilapors, central nervous system stimulants, corticosteroids, hormones, hypnotics, immunosuppressives, mucolytics, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, rhinitis treatment, sedatives, sexual hypofunction, tranquilizers and vitamins including B12.

[00042] As will be understood by those skilled in this art, various modifications may be made to the disclosed embodiment of the medicament respiratory delivery device 20 of this invention within the purview of the appended claims. For example, the passage 84 through the cartridge body 80 shown in Figure 8 may be bell-shaped or other shapes, although cylindrical is desirable, particularly with the relatively

low fluid pressure delivered by the pressure delivery device. Further, a conventional syringe assembly may be utilized having a conventional plunger and stopper; however, it is desirable to lock the stopper in the extended position such that the patient does not have to hold the stopper while opening the valve. Further, a conventional Schraeder valve operable at low pressures has been utilized in the medicament respiratory delivery device of this invention, although various types of valves and valving systems may be utilized. The Schraeder valve 56 may also be reversed, such that the valve stem 58 extends into the syringe barrel 46, wherein the valve is opened by engagement with the stopper 28. In this embodiment (not shown), the valve may be opened either by depressing the stopper 28 against the valve stem 58 to open the valve or more preferably, the medicament housing member 60 may be movable relative to the syringe barrel (as shown) to drive the valve stem 58 against the stopper 28 and open the valve, such that the valve may be opened on demand by the patient during use. As used herein, valve "inlet" and "outlet" will depend upon the orientation of the valve and is used merely to define the valve openings which receive and exhaust the fluid pressure. It is desirable however to use a valving system which may be easily opened on demand by the patient during use. Other pressure delivery devices may also be utilized, including collapsible bulbs as disclosed in the above-referenced co-pending application, wherein a separate pressure chamber is provided between the bulb and the valve with a one way check valve between the bulb and the pressure chamber. Further, other locking mechanisms may be utilized to releasably interconnect the plunger and stopper assembly 22 in the barrel and valve assembly 24 following pressurization or charging of the chamber 92 including, for example, bayonet-type connections, a separate locking member and interlocking detents and detent pockets.

[00043] Further, the cartridge may include only one polymeric burstable membrane, preferably at the outlet, wherein the membrane at the inlet is a pierceable film or a film which is removed prior to use. Other types of membranes may also be used to seal the medicament cartridge or medicament chamber of the housing, including "nonburstable" membranes, for example, which are preslit to open at a pressure of less than 10 atmospheres, preferably less than 5 atmospheres, and most preferably oriented at right angles. As used herein, the term "open" the membranes is intended to be generic to either busting or rupturing burstable membranes as disclosed herein or dilating preslit membranes. Further, although a replaceable medicament cartridge is desirable to permit reuse of the housing or dosing member, the cartridge may be eliminated by sealing the inlet and outlet of the housing chamber with membranes. Finally, although the medicament respiratory delivery device of this invention was developed for delivery of a powder medicament, the cartridge of this invention is suitable for delivery of a liquid or even a gaseous medicament and the barrel 46 may also contain a liquid medicament or diluent, wherein the cartridge includes a powder medicament. Having described a preferred embodiment of the medicament respiratory delivery device, the invention is now claimed, as follows.